

REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Claim 1 is amended to specify that the hollow pin is held in a colony picking position in which a distal end of the hollow pin is immersed in the medium and offset from the base of the sample container by an offset distance, and the animal cell colony is aspirated into the hollow pin while the distal end of the hollow pin is held in colony picking position. Support for the amendments to claim 1 can be found, *inter alia*, at page 17 of the specification, lines 14-28.

Claim 10 is amended to specify that the apparatus is equipped with a computer comprising an image processing software for identifying the location of the colonies, a control software for controlling the picking of the colonies by interacting with the image processing software, and a picking head which is movable relative to the apparatus bed under the control of the control software. Claim 10 is further amended to specify that the animal cell colonies are picked from the medium by at least one hollow pin *at an offset distance* and the control software of the computer is operable to control the apparatus for colony picking by: (i) capturing an image of the animal cell colony with the camera; (ii) performing image analysis with the image processing software to detect animal cell colonies, thus creating a list of target colonies; and (iii) assigning the apparatus to collect the target colonies with the control software, wherein the target colonies are picked by repeatedly performing the following actions specified by the control software: (a) aligning at least one hollow pin to an animal cell colony location in the pick list; (b) lowering the hollow pin to a colony picking position in which a distal end of the hollow pin is immersed in the medium and offset from the base of the sample container by an offset distance, and (c) aspirating the animal cell colony into the hollow pin while the distal end of the hollow pin is held in colony picking position. Support for the amendments to claim 10 can be found, *inter alia*, in the specification at page 12, lines 20-30; page 15, line 17 to page 16, line 9; page 16, lines 11-24; page 17, lines 14-21; and Figures 7 and 10-12.

Additionally, claims 1-3 and 10-13 are amended to correct formal matters. Specifically, the foregoing amendment replaces the phrase “moving to” in claim 1 with the phrase “aligning with”, and the term “plurality” in claims 1-3 and 10-13 with the phrase “at least one”. Further, claim 3 specifies that one hollow pin comprises a plurality of hollow pins. Support for the amendments to claims 1-3 and 10-13 can be found, *inter alia*, in the specification at page 12, lines 4-30, and Figures 6-7.

Claims 20-22 are also amended. The amendment to claims 20-22 incorporates step (e) of claim 1. Support for the amendment to claims 20-22 can be found, *inter alia*, at page 17 of the specification, lines 14-28.

New claims 23-35 are added. Claims 23-32 specify the range of the offset distance at which the animal cell colonies are picked by the hollow pin. Claim 33 specifies that one hollow pin comprises a plurality of hollow pins. Claims 34-35 specify that the drive mechanism is in the picking head and is not provided by the positioning motors. Support for new claims 23-35 can be found, *inter alia*, in the specification at page 5, line 12, page 12; lines 4-30; Figures 6-7; and claim 10 as previously presented. The section at page 12 in the specification describes an inner pin (item 64 in Figures 6-7), which is recessed inside the outer pin (item 62 in Figures 6-7) by a distance d1. The electric motor (item 60 in Figures 6-7) is connected to the inner pin such that the inner pin describes a rotary motion. The outer pin is recessed from the bottom of the sample container by a distance d2. Thus, the offset distance claimed in the present application is the sum of d1 and d2. The specification at page 12, lines 18-30, defines d1 as having values of 0.1 to 2.0 mm, and d2 as having values of 0.0 to 2.0 mm. Thus, the range of d1 + d2 is 0.1 to 4.0 mm.

As the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested. Upon entry of the foregoing amendments, claims 1-35 will be pending in the application, with claims 1 and 10 being the independent claims.

II. Interviews with the Examiner

Applicants thank Examiner Nathan Andrew Bowers for the courtesy extended in the personal interview held on October 12, 2006 with Applicants' representative, and the

telephone interview held on December 19, 2006. The claims presented herein and the following remarks reflect the issues that were discussed in the interviews.

III. The Rejections Under 35 U.S.C. § 103(a)

A. Rejection over Uber in view of Bienert

The Office Action, at pages 2-3, maintains the rejection of claims 10 and 21 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Uber *et al.*, *Biotechniques*, 11(5): 642-646 (1991 ("Uber")) in view of U.S. Patent Application Publication No. 20010019845 ("Bienert"). Applicants respectfully traverse this ground of rejection.

The Patent Office bears the initial burden of factually supporting any *prima facie* conclusion of obviousness under 35 U.S.C. § 103. The MPEP § 2142 sets forth the criteria necessary to satisfy this burden:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As discussed below, there is no *prima facie* case of obviousness, because none of these three criteria is satisfied.

1. Summary of the Claimed Invention

The presently claimed invention is directed to a method for automated picking of animal cell colonies. The method employs a picking head comprising at least one hollow pin to pick the colonies. The method comprises lowering at least one hollow pin to a colony

picking position in which a distal end of the hollow pin is immersed in the medium and offset from the base of the sample container containing the animal cell colonies *by an offset distance* and aspirating the animal cell colony into the hollow pin *while the distal end of the hollow pin is held in the colony picking position*.

Further, the invention is directed to an apparatus for picking animal cell colonies comprising a camera for capturing images, a computer comprising an image processing software for identifying the location of the colonies and a control software for controlling the picking of the colonies by interacting with the image processing software, and a picking head comprising at least one hollow pin connected to a drive that introduces a distal end of the hollow pin into the sample container *offset from the animal cell colony*, such that the animal cell colonies are picked from the medium by the hollow pin at *an offset distance*. The control software of the computer controls the apparatus for colony picking by: (i) capturing an image of the animal cell colony with the camera; (ii) performing image analysis with the image processing software to detect animal cell colonies, thus creating a list of target colonies; and (iii) assigning the apparatus to collect the target colonies with the control software. The target colonies are picked by repeatedly performing the following actions specified by the control software: (a) moving at least one hollow pin to an animal cell colony location in the pick list; (b) lowering the hollow pin to a *colony picking position in which a distal end of the hollow pin is immersed in the medium and offset from the base of the sample container by an offset distance*, and (c) aspirating the animal cell colony into the hollow pin *while the distal end of the hollow pin is held in colony picking position*.

The invention is also directed to methods of using the apparatus for identifying and picking animal cell colonies.

As stated during the interview, contact between the picking pin and the animal cell colony disrupts animal cell colonies and displaces surrounding colonies, and once the animal cell colonies are displaced, the possibility of aspirating the colony is lost.

The claimed methods and apparatus are specifically designed to pick animal cell colonies *while the distal end of the hollow pin is held in a picking position at an offset*

distance from the colonies during the picking procedure, such that **no contact** is created between the picking pin and the cell colony, animal cell colonies are not destroyed and surrounding cell colonies are not displaced from their position.

**2. The Cited References Fail to Teach Each
and Every Element of the Claimed Invention**

The primary reference, Uber, discloses a system that applies image processing and robotic techniques for automatically picking bacteria or yeast colonies from Petri dishes. Uber fails to disclose or suggest at least three elements of the claimed invention.

First, Uber does not disclose or suggest an apparatus for picking animal cell colonies. Rather, Uber discloses an apparatus for picking *bacteria or yeast colonies*. See Introduction at page 642. The picking of bacterial or yeast colonies is different from the picking of animal cell colonies, because animal cell colonies are greater in size and fewer in number than bacterial or yeast colonies. Thus, the picking mechanism used for bacteria or yeast colonies cannot necessarily be used for animal cell colonies. Second, Uber does not disclose or suggest an integrated imaging and picking robot. Instead, Uber discloses two separate systems: a) an imaging system to digitize and store the image of a dish and establish the coordinates of the colonies in the dish. See Imaging Procedure at page 643 and Figure 2; and b) a Hewlett-Packard Microassay System robot for colony picking. See Robotic System at page 644 and Figure 4. Third, Uber fails to disclose or suggest a non-contact picking apparatus, where the hollow pin is immersed in the medium and held in picking position offset from the cell colony “by an offset distance.” As discussed above, this “offset distance” allows colonies to be picked without disruption or displacement.

The Office Action recognizes deficiencies in the primary reference. Specifically, the Office Action acknowledges that Uber *does not expressly disclose a plurality of hollow pins connected to the picking head*. See pages 2-3. Nevertheless, the Office Action relies on the disclosure of Bienert for the teachings of an automatically controlled metering head comprising a plurality of micropipette tubes for the aspiration of fluids from a sample container and their disposition in a dispensing container. Bienert, however, does not remedy the deficiencies of Uber.

Bienert discloses a metering head for holding, moving and releasing fluid samples. Thus, Bienert fails to disclose or suggest two elements of the claimed invention. First, Bienert does not disclose or suggest a method and an apparatus for picking animal cell colonies. Instead, Bienert discloses an apparatus for picking *fluid samples*. See paragraphs [0002] and [0003] at page 1. Second, Bienert, like Uber, fails to disclose or suggest a non-contact picking apparatus. Thus, Bienert fails to remedy the deficiencies of Uber.

3. There is no Motivation or Suggestion to Combine the References

The present obviousness rejection improperly selects isolated teachings from the cited references and combines them in an effort to draw conclusions regarding the claimed invention, when there is no teaching, suggestion or motivation to do so.

For example, the Office Action at page 3 states that it would have been obvious to construct the apparatus of Uber with a picking head comprising a plurality of hollow pins capable of independently collecting cell samples using suction, and subsequently dispensing the samples at a different location. However, there would have been no motivation to combine the two cited references to devise a method and apparatus for picking animal cell colonies, as claimed in the present application, because these references are directed to different fields of endeavor: Uber discloses a method and apparatus for the picking of bacterial or yeast colonies, whereas the invention of Bienert is directed to a system for moving and releasing fluid samples. Because methods and apparatuses for the analysis of fluid samples are very different from those used for the picking of bacterial and yeast colonies, and neither is applicable for picking animal cell colonies, one of skill in the art would simply have no reason to modify the apparatus of Uber by inserting a picking head comprising multiple hollow pins, as disclosed by Bienert, to devise the non-contact method and apparatus for picking animal cell colonies claimed in the present application.

4. One of Skill in the Art Would Have no Expectation of Success

One of skill in the art would not have a reasonable expectation of success in modifying the references to arrive at the claimed invention for at least two reasons.

First, as stated above, methods and apparatuses for picking bacterial and yeast cell colonies or fluid samples cannot be used for animal cell colonies because of the different size and nature of animal cell colonies. Thus, the artisan skilled in the art would have no reasonable expectation of success in adapting the apparatus of Uber or the apparatus of Bienert for use in picking animal cell colonies.

Second, both Uber and Bienert fail to disclose or suggest a non-contact picking method and apparatus. Thus, the artisan skilled in the art would not expect that holding the distal end of a hollow pin in a colony picking position at an offset distance from the animal cell colony during the picking procedure would result in an effective aspiration of the animal cell colony into the hollow pin.

For at least these reasons, the rejection over Uber in view of Bienert under 35 U.S.C. § 103(a) is improper. Accordingly, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

B. Rejection Over Magnuson in view of Elverd

The Office Action, at pages 3-5, maintains the rejection of claims 1, 3, 10 and 13 under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent Application Publication No. 2003/0179916 A1 (“Magnuson”) in view of U.K. Patent Application No. 2310006 A (“Elverd”). Applicants respectfully traverse this ground of rejection.

The Office has failed to establish a *prima facie* case of obviousness, because, as detailed below, none of the criteria necessary to satisfy the burden of factually supporting a *prima facie* conclusion of obviousness under 35 U.S.C. § 103 is satisfied.

1. The Cited References Fail to Teach Each and Every Element of the Claimed Invention

The primary reference, Magnuson, discloses a method and apparatus for picking animal cell colonies comprising contacting a picking pin to the base of a sample container and aspirating, or scraping and then aspirating, the cell colonies from the surface of a growth

substrate. See paragraphs [0024] at page 3 and [0067] at page 6. Magnuson specifically teaches:

“a tip is designed with regard to the mechanism by which a colony or cell is to be removed from a growth substrate. For example, if the removal is to be exclusively via aspiration techniques, a tip can be designed such that it can form an essentially airtight seal with the colony or cell, making the removal of the cell or colony more efficient. Alternatively, if the removal is to be via a physical scraping motion, a tip can be designed with a suitable scraping surface adapted to scrape a colony from the growth substrate. If a tip is to operate via a combined aspiration and scraping technique, the tip can be formed with both a scraping edge, which is formed of angles and dimensions that still permit the tip to form a seal with a cell or colony to be isolated.”

See Paragraph [0127] at page 11 (Emphasis added).

Thus, Magnuson fails to disclose or suggest two essential elements of the claimed invention: **First**, Magnuson does not disclose or suggest a method and an apparatus for picking animal cell colonies, where animal cell colonies are picked and aspirated into the hollow pin *while the hollow pin is held in a colony picking position in which a distal end of the hollow pin is immersed in the medium and is at an offset distance from the colonies*, such that there is **no contact** between the pin and the animal cell colony during the entire picking procedure. **Second**, with regard to the apparatus, Magnuson fails to disclose or suggest an apparatus comprising an image processing software and a control software, where the control software controls the colony picking position of the hollow pin, such that *the distal end of the hollow pin is offset from the base of the sample container containing the animal cell colony by an offset distance during the picking procedure*.

Rather, Magnuson teaches that the contact between the picking pin and the colony is necessary and provides an apparatus specifically designed for contact colony picking, by physical scraping motion or forming an airtight seal of the tip with the colony. See page 3, paragraph [0024], and page 11, paragraph [0127]. Thus, Magnuson teaches away from the claimed invention by failing to recognize that contact between the picking pin and the animal cell colony disrupts the cell colony and displaces surrounding colonies.

The Advisory Action states that *although Magnuson discloses that the hollow pin makes contact with the colonies during aspiration*, the hollow pin is positioned at an offset distance from the cells at some point during the entire picking procedure.

Further, with regard to the apparatus recited in claim 10, the Advisory Action alleges that *the positioning motors disclosed by Magnuson are fully capable of positioning the hollow pin at any distance relative to the cell colony*, since Magnuson discloses all the structures recited in the claim.

As stated above, the main feature of the method and apparatus recited in the present claims is that *the distal end of the hollow pin is held at an offset distance from the colonies during the picking procedure*, such that **no contact** is created between the picking pin and the cell colony during aspiration, animal cell colonies are not destroyed and surrounding cell colonies are not displaced from their position. Clearly, as recognized in the Advisory Action, Magnuson does not disclose or suggest the specifically claimed features of the present invention.

Further, claim 10 has been amended to explicitly recite that the control software controls the colony picking position of the hollow pin, such that the distal end of the hollow pin is offset from the base of the sample container containing the animal cell colony by an offset distance during the entire picking procedure. Magnuson fails to disclose or suggest such a feature.

Elverd does not remedy the deficiencies of Magnuson. Elverd discloses a mechanical head comprising a plurality of pins for transferring biological samples. Elverd teaches that *“whenever a piston in the pneumatic actuator is fired it hits a sprung pin in the 96 pin picking head, which is fired forwards, enabling it to pick a colony.”* See bottom paragraph at page 2 (Emphasis added). Thus, Elverd, like Magnuson, fails to disclose or suggest a method and an apparatus for picking animal cell colonies, where animal cell colonies are picked and aspirated into the hollow pin *while the hollow pin is held in a colony picking position in which a distal end of the hollow pin is immersed in the medium and is at an offset distance from the colonies*, such that there is **no contact** between the pin and the animal cell colony

during the picking procedure. Further, Elverd fails to disclose or suggest an apparatus comprising an image processing software and a control software, where the control software controls the colony picking position of the hollow pin, such that *the distal end of the hollow pin is offset from the base of the sample container containing the animal cell colony by an offset distance during the picking procedure.*

3. There is no Motivation or Suggestion to Combine the References

The Office Action at pages 4-5 states that “*it would have been obvious to ensure that the invention disclosed by Magnuson contained a plurality of hollow pins each individually aligned with the characteristic spacing of the wells located in the dispensing container.*” The Office Action further states that “*the use of hollow tubes correlating to multiple wells reduces cross contamination since different tubes are used to collect different samples*

However, this alleged motivation to modify the apparatus disclosed by Magnuson is not found in the prior art. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) holds that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not be based on Applicant’s disclosure.

Furthermore, there would have been no motivation to combine Magnuson and Elverd to devise a non-contact method and apparatus for picking animal cell colonies, because none of the cited references discloses a method and apparatus for picking animal colonies without creating any contact between the picking pin and the colonies during aspiration. Indeed, both Magnuson and Elverd teach against an apparatus comprising hollow pins that pick animal cell colonies from the medium while the distal end of the hollow pin is held in a colony picking position at an offset distance from the colonies. Both references fail to disclose or suggest a method where there is no contact between the pin and the animal cell colony during the picking procedure. One of skill in the art would simply have no reason or rationale to modify the apparatus and method disclosed by Magnuson or the apparatus and method disclosed by Elverd to devise a non-contact method and apparatus for picking animal cell colonies. Thus, the cited references do not support the obviousness rejection.

4. One of Skill in the Art Would Have no Expectation of Success

One of skill in the art would not have a reasonable expectation of success in modifying the references to arrive at the claimed invention because, as stated above, the cited references fail to disclose or suggest a non-contact picking method and apparatus. Thus, the artisan skilled in the art would not expect that holding the distal end of a hollow pin in a colony picking position at an offset distance from the colonies during the picking procedure would result in an effective aspiration of the animal cell colony into the hollow pin.

For at least the reasons stated above, this rejection is improper. Accordingly, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

**C. Rejection over Magnuson in view of Elverd
and further in view of Sogi or Parekh**

The Office Action at pages 6-7 maintains the rejection of claims 4, 11 and 12 under 35 U.S.C. § 103(a) as being unpatentable over Magnuson in view of Elverd and further in view of U.S. Patent No. 4,210,724 ("Sogi").

Further, at pages 7-10, the Office Action maintains the rejection of claims 4, 7-9, 14-17 and 20 under 35 U.S.C. § 103(a) as being unpatentable over Magnuson in view of Elverd and further in view of U.S. Patent No. 6,064,754 ("Parekh").

The inability of Magnuson and Elverd to teach or suggest the invention of claims 1, 3, 10 and 13 is demonstrated above. The additional references, Sogi and Parekh, do not remedy the deficiencies of Magnuson and Elverd. Rather, Sogi is directed to an apparatus for liquid disposal and distribution for use in an automatic culture, and Parekh is drawn to computer-assisted methods and apparatus for identifying, selecting and characterizing biomolecules in a biological sample. Both references fail to teach or suggest the non-contact picking method and apparatus claimed in the present application. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 4, 11 and 12 and claims 4, 7-9, 14-17 and 20 under 35 U.S.C. § 103(a).

CONCLUSION

All of the stated grounds of rejections have been properly traversed or rendered moot. Therefore, the present application is now in condition for allowance, and an early notice to that effect is earnestly solicited.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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